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Longitudinal structural brain development and externalizing behavior in adolescence

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Background: Cross-sectional studies report relations between externalizing behavior and structural abnormalities in cortical thickness of prefrontal regions and volume reductions in subcortical regions. To understand how these associations emerge and develop, longitudinal designs are pivotal. **Method:** In the current longitudinal study, a community sample of children, adolescents and young adults ($N = 271$) underwent magnetic resonance imaging (MRI) in three biennial waves (680 scans). At each wave, aspects of externalizing behavior were assessed with parent-reported aggression and rule-breaking scores (Child Behavior Checklist), and self-reported aggression scores (Buss-Perry Aggression Questionnaire). Regions of interest (ROIs) were selected based on prior research: dorsolateral prefrontal (dlPFC), orbitofrontal (OFC), anterior cingulate cortex (ACC), insula, and parahippocampal cortex, as well as subcortical regions. Linear mixed models were used to assess the longitudinal relation between externalizing behavior and structural brain development. Structural covariance analyses were employed to identify whether longitudinal relations between ROIs (maturational coupling) were associated with externalizing behavior. **Results:** Linear mixed model analyses showed a negative relation between parent-reported aggression and right hippocampal volume. Moreover, this longitudinal relation was driven by change in hippocampal volume and not initial volume of hippocampus at time point 1. Exploratory analyses showed that stronger maturational coupling between prefrontal regions, the limbic system, and striatum was associated with both low and high externalizing behavior. **Conclusions:** Together, these findings reinforce the hypothesis that altered structural brain development coincides with development of more externalizing behavior. These findings may guide future research on normative and deviant development of externalizing behavior. **Keywords:** Externalizing behavior; aggression; adolescence; structural MRI; longitudinal design.

Introduction

Adolescence, the transition period between childhood and adulthood, is marked by substantial cognitive, affective, and social development (Dahl & Gunnar, 2009). An interesting adolescent-specific pattern concerns the increase in risk-taking, sensation seeking, and novelty seeking, which is often interpreted as a normative pattern in the path toward autonomy and identity development (Crone, Duijvenvoorde, & Peper, 2016; Pfeifer & Peake, 2012). At the same time, deviant behavior such as substance abuse, aggression, and delinquency emerge in adolescence in a subset of individuals (Fairchild, Goozen, Calder, & Goodyer, 2013; Moffitt, 2018), but why and how this occurs is not yet well understood. Although research has shown consistent patterns in developmental changes in brain structure across adolescence (Herting et al., 2018; Mills et al., 2016; Tamnes et al., 2017), few studies examined how the developmental pathway to externalizing behavior is associated with changes in brain development.

Longitudinal studies have demonstrated that adolescent brain development is associated with continuing changes in cortical and subcortical gray matter (Vijayakumar et al., 2016; Wierenga et al., 2014). Multisample studies have confirmed that the overall patterns are comparable across datasets and cultures, providing consistent evidence for cortical gray matter reductions across adolescence, continuing into young adulthood – with the speed of change being region-dependent (Tamnes et al., 2017). A crucial, but poorly understood question concerns how these developmental patterns are related to individual differences in behavioral development, which can only be directly examined using longitudinal designs. Although longitudinal studies do not allow for the test of causality, they do provide a better understanding of how patterns coincide within individuals, and how early markers predict later behavioral outcomes (King et al., 2017).

Our current understanding of the neurobiological correlates of externalizing behavior is, however, mainly derived from cross-sectional studies comparing clinical samples to healthy controls. These studies showed that externalizing behavior in adolescents (including aggression, psychopathy, and

Conflict of interest statement: No conflicts declared.

conduct problems) is related to volumetric reductions in prefrontal regions, such as the orbitofrontal (OFC), dorsolateral prefrontal (dlPFC) and anterior cingulate (ACC) cortices (for a meta-analysis, see Yang & Raine, 2009), and also to volumetric reductions in subcortical regions, like the striatum, amygdala, and hippocampus (Noordermeer, Luman, & Oosterlaan, 2016; Wallace et al., 2014). Externalizing problems, like many other psychiatric symptoms, exist on a continuum in the general population (Garvey, Avenevoli, & Anderson, 2016). Instead of using a categorical approach, which is defined by cut-offs between adaptive and maladaptive behavior (e.g., diagnostic criteria), a dimensional approach of psychopathology may better capture the variation between mental health and mental illness and may therefore provide novel insights in brain-behavior association across development (Casey, Oliveri, & Insel, 2014).

There are a few longitudinal studies that examined the relation between structural brain development and externalizing behavior in community samples. In a study including children and adolescents (6–18 years), Ameis et al. (2014) showed that externalizing behavior was negatively associated with cortical thickness in OFC and cingulate cortex, but they did not find a relation with hippocampus or amygdala volume. Findings from a three-wave longitudinal study showed that groups of adolescents with distinct developmental patterns of externalizing behavior showed different developmental structural brain changes, such that a group with desisting conduct problems showed an attenuation of the typical pattern of cortical thinning in dlPFC and ACC compared to groups with stable low or intermediate levels of externalizing behavior (Oostermeijer et al., 2016). Furthermore, this 'desisting' group showed an exaggeration of growth in hippocampal volume (Oostermeijer et al., 2016). Yet, a recent large-scale longitudinal study focusing on late childhood reported that higher levels of externalizing behavior was predictive of attenuated maturation of total subcortical volume (Muetzel et al., 2017). Taken together, existing longitudinal findings to date are inconsistent both in regions that are associated with externalizing behavior as well as the direction of this association.

Structural neuroimaging studies also examined associations between brain regions to test relations between structural networks and cognitive and affective processes, which potentially reveal more about distributed networks and their behavioral associations (Evans, 2013). Structural covariance refers to correlations between properties of brain regions across individuals (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013). Longitudinal designs allow for examination of maturational coupling (i.e., patterns of correlated change across subjects), which may reflect coordinated development between regions (Alexander-Bloch et al., 2013). In line with this framework, Ameis et al. (2014) demonstrated that orbitofrontal-amygdala structural network properties were associated with externalizing behavior. Specifically, low levels of externalizing behavior were associated with stronger maturational coupling within the OFC-amygdala network.

We aimed to test the association between brain developmental patterns and externalizing behavior, with a threefold focus: (a) confirm the longitudinal relations between externalizing behavior and cortical brain structure, specifically in the dlPFC, OFC, and ACC (Oostermeijer et al., 2016), (b) test the longitudinal developmental relations between externalizing behavior and subcortical brain structures in more detail (Ameis et al., 2014; Muetzel et al., 2017; Oostermeijer et al., 2016), and (c) examine how maturational coupling between volume of these brain regions relate to externalizing behavior (Ameis et al., 2014). For this purpose, we tested participants from a community sample between ages 8 and 29 years, who were scanned at three occasions, each separated by a 2-year-interval. Aspects of externalizing behavior were measured with parent-report measures of aggression and rule-breaking (i.e., Child Behavior Checklist (CBCL) and with a self-reported measure of aggression (Buss-Perry Aggression Questionnaire (BPAQ)). Both questionnaires have previously been shown to be valid and reliable (Achenbach & Rescorla, 2000; Buss & Perry, 1992).

We hypothesized that the development of prefrontal cortical regions negatively coincides with externalizing behavior. Hence, we expected that higher levels of externalizing behavior would be associated with attenuated cortical thinning in dlPFC, OFC, and ACC (Ameis et al., 2014; Oostermeijer et al., 2016). Moreover, we expected a negative relation between externalizing behavior and subcortical development, specifically in striatum, hippocampus, and amygdala volume (Muetzel et al., 2017; Wallace et al., 2014). Finally, we examined the relation between maturational coupling and externalizing behavior. Although exploratory in nature, we expected that low externalizing behavior was associated with stronger maturational coupling between prefrontal regions and subcortical regions (Ameis et al., 2014).

Methods and materials

Participants and procedure

This study was part of the longitudinal research project *BrainTime* (Becht et al., 2018; Bos, Peters, van de Kamp, Crone, & Tamnes, 2018; Peper, Braams, Blankenstein, Bos, & Crone, 2018; Peters & Crone, 2017; Schreuders et al., 2018; Wierenga et al., 2018), conducted in Leiden, The Netherlands. For this study, a community sample of children, adolescents, and young adults were recruited from local schools and advertisement. At the first time point (TP1), 299 participants were included (ages: 8–25 years; 146 males). All participants were fluent in Dutch, right-handed, and had normal or

corrected-to-normal vision. Inclusion criteria were the absence of neurological or mental health problems or the use of psychotropic mediation at TP1. One participant reported to have an attention deficit disorder diagnosis at TP1 and was therefore excluded.

Participants were invited to participate in three consecutive assessment waves approximately every 2 years. Intelligence was assessed at TP1 and TP2 using two subtests of age-appropriate Wechsler Intelligence Scales (TP1: Similarities and Block Design; TP2: Vocabulary and Picture Completion). All participants had an estimated overall IQ >80. The institutional Review Board at Leiden University Medical Center approved the study. Informed consent was obtained from participants or from parents in case of minors at each time point. Participants received a financial reimbursement for their participation in the study.

Materials

Parent-reported aggression and rule-breaking. The CBCL (Achenbach & Rescorla, 2000) is a parent-report instrument that was used to assess levels of aggressive behavior and rule-breaking in children and adolescents under age 18. The CBCL is a well-validated questionnaire and widely used to assess a broad range of behavior problems in children (ages 6–18) as observed in the previous 2 months. In this study, we used the raw scores of the aggressive behavior and rule-breaking scales. The aggressive behavior scale consists of 18 items, and the rule-breaking scale of 17 items. Parents were asked to rate each statement on a 3-point scale ranging from 'not true' to 'very true/often true'. Cronbach's alpha for aggressive behavior was good for all three TPs (α = .79 –.83). Cronbach's alpha for rule-breaking was poor at TP1 (α = .50) and acceptable at TP2 (α = .66) and TP3 (α = .72).

Self-reported aggression. The BPAQ (Buss & Perry, 1992) is a self-report measure of aggressive tendencies and comprises 29 items. The BPAQ distinguishes four subscales: physical aggression (e.g., 'If someone hits me, I hit back'), verbal aggression (e.g., 'I tell my friends openly when I disagree with them'), anger (e.g., 'I have trouble controlling my temper'), and hostility (e.g., 'When people are especially nice, I wonder what they want'). Participants indicated on a 7-point scale the degree to which each item characterized them (ranging from 'extremely uncharacteristic of me' to 'extremely characteristic of me'). The cumulative score on total aggression was used for analyses. Cronbach's alpha was good across all TPs (α = .81–.86). The BPAQ data from the project have been reported previously in relation to sex steroid hormones and diffusion weighted imaging measures of white matter (Peper, De Reus, Van Den Heuvel, & Schutter, 2015; Peper et al., 2018).

Image acquisition and analysis

Structural magnetic resonance images (MRI) were acquired on the same 3 Tesla Philips Achieva whole body scanner, with a standard 32-channel whole-head coil. T1-weighted anatomical scans were obtained at each time point (TR = 9.8 ms, TE = 4.6 ms, flip angle = 8°, 140 slices, 0.875 mm × 0.875 mm × 1.2 mm, and FOV=224 × 177 × 168 mm). Scan time for this sequence was 4 min 56 s. There were no major scanner hardware or software upgrades during the data collection period. A radiologist reviewed all T1-weighted scans; no anomalous findings were reported.

Image processing

Whole-brain volumetric segmentation and cortical surface reconstruction was performed using the longitudinal pipeline of FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu/). The technical details and specific processing steps are described elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl et al., 2002; Reuter, Schmansky, Rosas, & Fischl, 2012). Detailed post-processing quality control was performed on all scans (see Appendix S1 for details). For each scan, volumetric estimates for subcortical regions were extracted per hemisphere. Parcellation of the cerebral cortex into gyral regions was performed using the Desikan-Killiany-Tourville atlas (Klein & Tourville, 2012). Per hemisphere, 31 cortical regions were labeled.

Regions of interest

Based on previous research on externalizing behavior, we selected the following regions of interest (ROIs): the OFC, the dlPFC, the ACC, the insula, and the parahippocampal cortex. For each hemisphere, the mean cortical thickness was created by combining the following parcellation units: OFC, medial and lateral OFC; dlPFC, superior frontal, rostral middle frontal and caudal middle frontal cortex; ACC: rostral and caudal ACC. For the cortical thickness index, we took the size of each included ROI into account. For example, we calculated cortical thickness of the OFC as follows:

$$\frac{(CT_{\text{medialOFC}} * SA_{\text{medialOFC}}) + (CT_{\text{lateralOFC}} * SA_{\text{lateralOFC}})}{(SA_{\text{medialOFC}} + SA_{\text{lateralOFC}})}$$

Additionally, we investigated the following subcortical volumes: amygdala, hippocampus, caudate, putamen, pallidum, nucleus accumbens, and thalamus.

Statistical analyses

Statistical analyses were performed using SPSS 23.0 (IBM SPSS Statistics, IBM Corporation) and R 3.2.0 (R Core Team, 2014). To examine reliability over time, we calculated intra-class correlations using SPSS (see Table S1). To examine the developmental trajectory of parent-reported aggression scores, parent-reported rule-breaking scores, and self-reported aggression scores we used mixed model analyses, using the *nlme* package in R (Pinheiro, Bates, DebRoy, & Sarkar, 2014) (see Appendix S1 for model selection procedure). Next, we examined the longitudinal relations between parent-reported aggression, parent-reported rule-breaking, self-reported aggression and thickness of the specified cortical ROIs, and volume of the subcortical ROIs. Each ROI was added to the best age model, separately. Note, that sex did not improve growth model fit of parent-reported aggression, parent-reported rule-breaking, nor self-reported aggression. To control for age and sex effects on structural brain measures, we used regression residuals of MRI measures in our mixed models to predict externalizing behavior. That is, we first assessed the best age model for each MRI variable and tested whether sex improved model fit. Next, we extracted the regression residuals for the best fitting growth model for each MRI variable. The model below outlines our general mixed model:

$$Y_{ij} = \text{age}_{ij} + \text{residual MRI}ij + 1|\text{Subject}$$

The *i* subscript denotes subject, the *j* denotes TP. Additionally, we examined whether an interaction between age and MRI explained additional variance to the models. For significant findings, we additionally tested whether initial level or brain development contributed to development of externalizing behavior. To do so, we added TP1 and change related to TP1 as predictors in the mixed model analyses (i.e., indices of TP1, TP2, and TP3 minus index of TP1). Also, for these indices, we used regression residuals based on the best fitting growth

model. The model below outlines our mixed model using initial level of the MRI variable (residual_baselineMRI) and change level of the MRI variable (residual_changeMRI):

$$Y_{ij} = \text{age}_{ij} + \text{residual\_baseline MRI}_i + \text{residual\_change MRI}_{ij} + 1|\text{Subject}$$

The *i* subscript denotes subject, the *j* denotes TP.

Additional analyses on cortical volume and cortical surface area are reported in the supplement (Table S2-S4).

To control for multiple comparisons, we used a Bonferroni correction procedure adjusted for correlated variables (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm) (Perneger, 1998; Sankoh, Huque, & Dubey, 1997). The average correlation between cortical thickness variables (five ROIs for both hemispheres) was $r = 0.53$, yielding a significance level for α (2-sided adjusted) = .018 for cortical thickness analyses. The average correlation between subcortical volumes (seven ROIs for both hemispheres) was $r = 0.40$, which resulted in an α (2-sided adjusted) = .010 for analyses on subcortical volume.

Finally, we explored whether maturational coupling in MRI volume measures were related to parent-reported aggression, parent-reported rule-breaking, and self-reported aggression scores by using anatomical correlations (Wierenga, Sexton, Laake, Giedd, & Tamnes, 2017). This method assesses the inter-regional anatomical associations by defining the statistical similarity between pairs of ROIs. To investigate maturational coupling, we used individual slopes for each ROI assessed over TPs. Hence, for each individual, we extracted the random slope from the best fitting age model using linear mixed models. Note that for the maturational coupling analyses, we only used participants with MRI data of all three TPs. The Pearson correlation coefficient between rates of change in any two regions (i.e., slope) *i* and *j* was assessed. Next, differences in correlations were compared between groups of high and low dimensions of externalizing behavior using permutation testing (see Appendix S1). Groups were defined using median split across all three TPs (median parent-reported aggression: 4.17; median parent-reported rule-breaking: 1.93; median self-reported aggression 86.00).

Results

Table 1 summarizes the sample characteristics. After quality control, we included 271 participants who had at least one MRI scan of good quality and available questionnaire data (total number of scans = 680). For the analyses concerning parent-reported aggression and rule-breaking we used data of participants that had CBCL data at least at one TP and were younger than 18 years old at TP3 ($n = 147$). For the analyses on self-reported aggression, we used participants who had Buss-Perry aggression scores on at least at one TP ($n = 269$). For the maturational coupling analyses, 69 participants were included for parent-reported aggression and parent-reported rule-breaking, and 168 participants for self-reported aggression.

Correlational analyses showed that self-reported aggression scores were positively correlated with parent-reported aggression scores (TP1: $r = 0.49$, $p < .001$; TP2: $r = 0.42$, $p < .001$; TP3: $r = 0.45$, $p < .001$) and parent-reported rule-breaking scores (TP1: $r = 0.37$, $p < .001$; TP2: $r = 0.33$, $p < .001$; TP3: $r = 0.37$, $p < .001$). Parent-reported aggression scores and rule-breaking scores correlated positively at each TP ($r = 0.58$–0.63).

Developmental trajectory of externalizing behavior

In Figure 1a-c, the developmental trajectories of parent-reported aggression, rule-breaking, and self-reported aggression are depicted as a function of age. For parent-reported aggression and rule-breaking, we found an increase across adolescence [Aggression (Age[1]): b = 7.96, $t_{(247)}$=2.59, $p = .01$; Rule-breaking (Age[1]): b = 14.00, $t_{(247)}$=7.00, $p < .001$]. Adding a random slope effect improved model fit for rule-breaking only, showing that for rule-breaking individuals differ both in intercept and developmental pattern. For self-reported aggression scores, the random intercept model fitted best. Adding a main effect of sex and/or an interaction effect with sex did not improve model fit for parent-reported aggression or, rule-breaking or, self-reported aggression (see Table S5 for model fit indices).

Longitudinal relation between parent-reported aggression and rule-breaking scores with cortical thickness and subcortical volumes

Mixed model analyses showed a longitudinal relation between parent-reported aggression scores with right hippocampus volume (residuals) (b = −7.34, $t_{(178)} = -2.87$, $p = .005$) and left pallidum volume (residuals) (b = 6.24, $t_{(178)} = 2.41$, $p = .017$) (Table S6). The latter effect was, however, not significant when correcting for multiple comparisons. As depicted in Figure 2, larger right hippocampus

Table 1 Sample characteristics

	TP1		TP2		TP3	
	M (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)	*n*
Age	14.13 (3.68)	271	15.99 (3.58)	263	18.09 (3.67)	254
Parent-report (CBCL)						
Aggression	3.96 (3.28)	134	3.82 (3.24)	141	4.66 (3.89)	135
Rule-breaking	1.43 (1.61)	134	1.76 (2.06)	141	2.65 (2.63)	135
Self-report (BPAQ)						
Aggression	84.38 (18.93)	253	87.38 (18.17)	245	87.43 (20.24)	240
Anatomical scan		238		226		219
Females/males		129/109		119/107		120/99

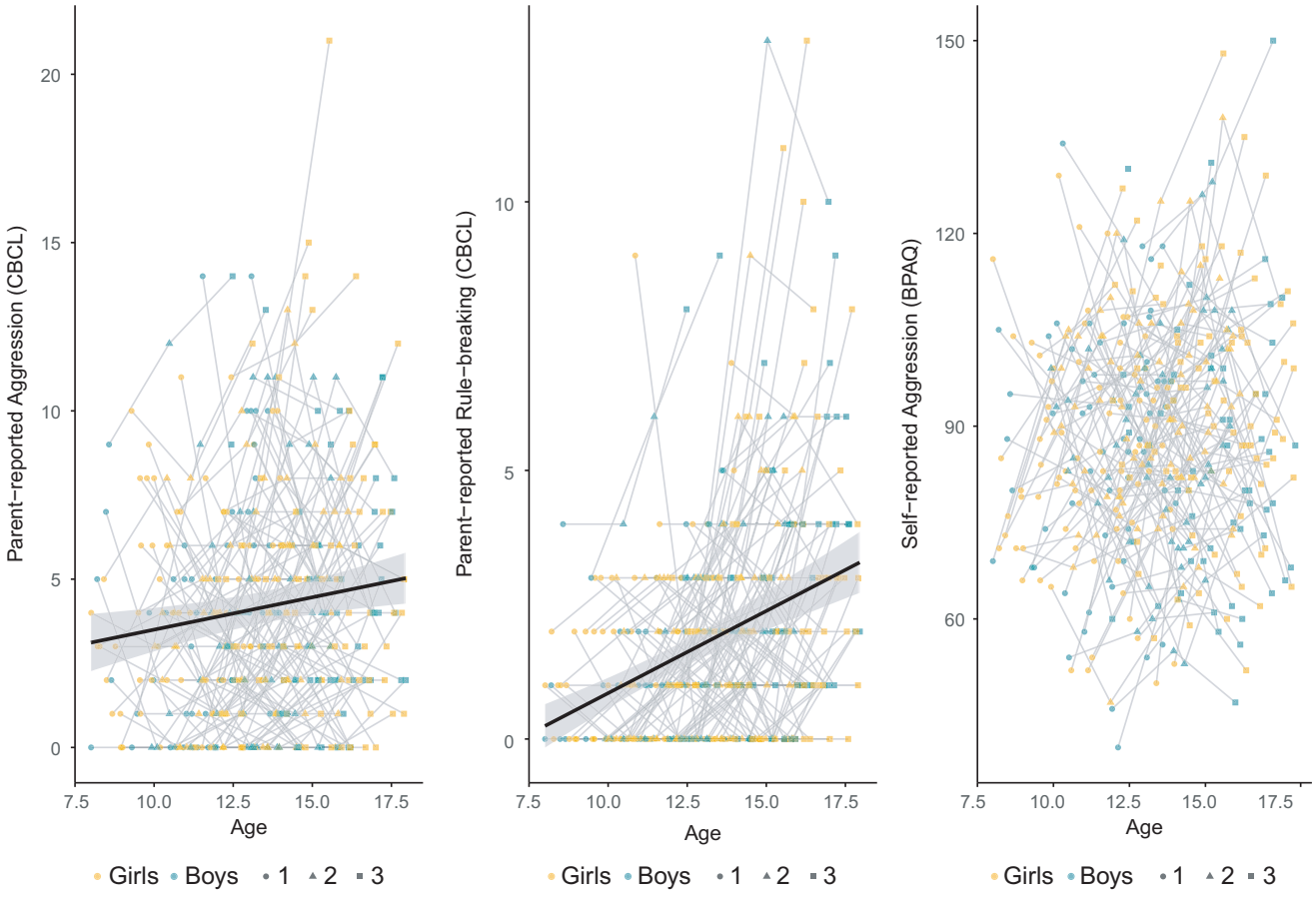

Figure 1 Developmental trajectories of (A) parent-reported aggression, (B), parent-reported rule-breaking, and (c) self-reported aggression. The line represents the optimal fitting model, shade represents 95% confidence interval. Lines represent individual participants, and participants who were measured once are represented by dots. Note, circle is TP1, triangle is TP2 and square is TP3

volume was associated with lower parent-reported aggression scores. In contrast, larger left pallidum volume was associated with higher parent-reported aggression scores (Figure S1). Note that when we replaced outliers ($Z \geq 3.0$) to 3 standard deviations from the mean, similar results were obtained. Adding age by ROI interactions did not improve model fit.

Next, we assessed whether the above-described significant relations between parent-reported aggression scores and regional brain indices were related to *change* relative to TP1 in subcortical volume or to initial level of these regional brain indices at TP1. Follow-up mixed model analyses showed that these relations were driven by *change* in right hippocampal volume (b = −7.11, $t_{(166)} = -2.48$, $p = .014$) and *change* in left pallidum volume (b = 6.31, $t_{(166)} = 2.20$, $p = .029$) (Table S7). Decreases in right hippocampal volume relative to TP1 were associated with increases in parent-reported aggression, independent of hippocampus volume at TP1. Increases in left pallidum volume relative to TP1 were associated with increases in parent-reported aggression, independent of level of pallidum volume at TP1.

For parent-reported rule-breaking scores, mixed models revealed a longitudinal relation between right OFC (b = −2.88, $t_{(178)} = -1.97$, $p = .050$) and left dlPFC thickness (b = −2.93, $t_{(178)} = -2.01$, $p = .046$), but neither of these effects survived correction for multiple comparisons (Figure S2 and Table S8). Follow-up mixed model analyses revealed that these longitudinal associations were driven by change in right OFC (b = −8.40, $t_{(165)} = -5.02$, $p < .001$) and left dlPFC thickness (b = −8.89, $t_{(165)} = -5.38$, $p < .001$) (Table S7). These results indicate that thinning in these regions and decreases in rule-breaking behavior are associated, independent of initial level of cortical thickness at TP1. Note that when we replaced outliers ($Z \geq 3.0$) to 3 standard deviations from the mean, similar results were obtained.

Longitudinal relation between self-reported aggression scores with cortical thickness and subcortical volumes

For self-reported aggression, the mixed model analyses revealed negative relations between self-reported aggression scores and left thalamus volume (b = −29.15, $t_{(364)} = -2.24$, $p = .026$), right putamen volume (b = −26.64, $t_{(364)} = -2.04$, $p = .042$), and right caudate volume (b = −27.87, $t_{(364)} = -2.17$,

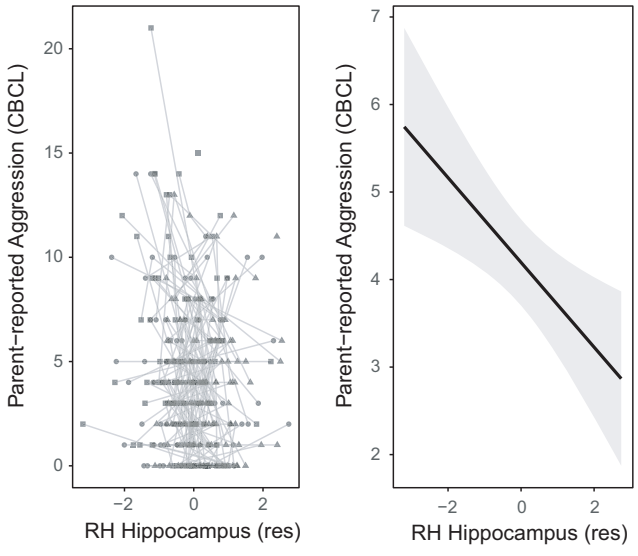

Figure 2 Mixed model analyses for the longitudinal relation between parent-reported aggression and hippocampal volume. Left panel represents individual data for three TPs for parent-reported aggression and hippocampal volume. Right panel depicts predicted model for parent-reported aggression and hippocampal volume (residuals). Note, circle is TP1, triangle is TP2 and square is TP3

p = .031)(Figure S3; Table S9). None of these relations survived correction for multiple comparisons. Also for self-reported aggression, adding an interaction term between age and ROIs did not improve model fit. Note that when we replaced outliers ($Z \geq 3.0$) to 3 standard deviations from the mean, similar results were obtained.

Follow-up analyses to examine whether development of self-reported aggression coincided with *change* in subcortical ROIs relative to TP1 or to level of these ROIs at TP1 revealed that the relation between self-reported aggressive behavior in right caudate volume was driven by *change* in right caudate volume (b = −36.86, $t_{(353)} = -2.55$, p = .011). That is, decreases in right caudate volume were associated with decreases in self-reported aggression regardless of initial level of right caudate volume at TP1. For right putamen volume and left thalamus volume, neither *change* nor initial level of these brain indices was significantly associated with developmental trajectories of aggressive behavior (Table S7).

Group differences in maturational coupling

We further explored whether maturational coupling between slopes of MRI volume measures were related to parent-reported aggression, parent-reported rule-breaking, and self-reported aggression scores. Figure 3 depicts the difference matrix that was derived from the subtraction of the correlated rates of anatomical change for high parent-reported Aggression group from the matrix of correlated rates of anatomical change for the low parent-reported Aggression group. Differences between groups (High vs. Low parent-reported Aggression Group) are depicted in the lower half of the matrix. Permutation testing showed that three correlations of anatomical change differed significantly between groups. Two correlations between rates of anatomical change were stronger in the high parent-reported Aggression group; left pallidum volume with left putamen volume and right thalamus volume with left putamen volume. The correlation between right hippocampal volume and right ACC volume was stronger in the low parent-reported Aggression group (see Figure S4).

Also, for parent-reported rule-breaking groups, permutation testing showed three significant differences between correlations of anatomical change between groups (Figure 4). Again, the correlations between left pallidum volume and left putamen volume, as well as left pallidum volume and left caudate volume, were stronger in the high parent-reported rule-breaking group. For the low parent-reported rule-breaking group, the correlation between right hippocampal volume and left pallidum volume was stronger (Figure S5).

Median split analyses on self-reported aggression showed five significant differences between maturational coupling in the high versus low group (Figure 5). Four correlations were stronger in the high self-reported aggression group: left amygdala volume with left ACC volume, right OFC volume with right insula volume, left pallidum volume with right thalamus volume, and left pallidum volume with right caudate volume. The correlation between left dlPFC volume and left ACC volume was stronger in the low self-reported aggression group (Figure S6).

Discussion

This study tested the relation between externalizing behavior and cortical and subcortical brain development in a typically developing sample. The behavioral analyses demonstrated an increase in parent-reported aggression and rule-breaking across adolescence, consistent with prior studies showing that adolescence is not only an important transition period for novelty seeking, impulsiveness, and sensation seeking (Crone et al., 2016), but also a period in which disruptive-behavior disorders emerge (Moffitt, 2018). Self-reported aggression scores, however, showed a stable pattern across age, but with large individual differences. An important question we addressed was whether individual trajectories of externalizing behavior were associated with individual differences in brain development; a question for which longitudinal designs are pivotal. This study yielded two main findings: (a) right hippocampal volume was negatively associated with parent-reported aggression, and (b) structural maturational coupling between regions within striatum, limbic system, and prefrontal regions were associated with externalizing behavior.

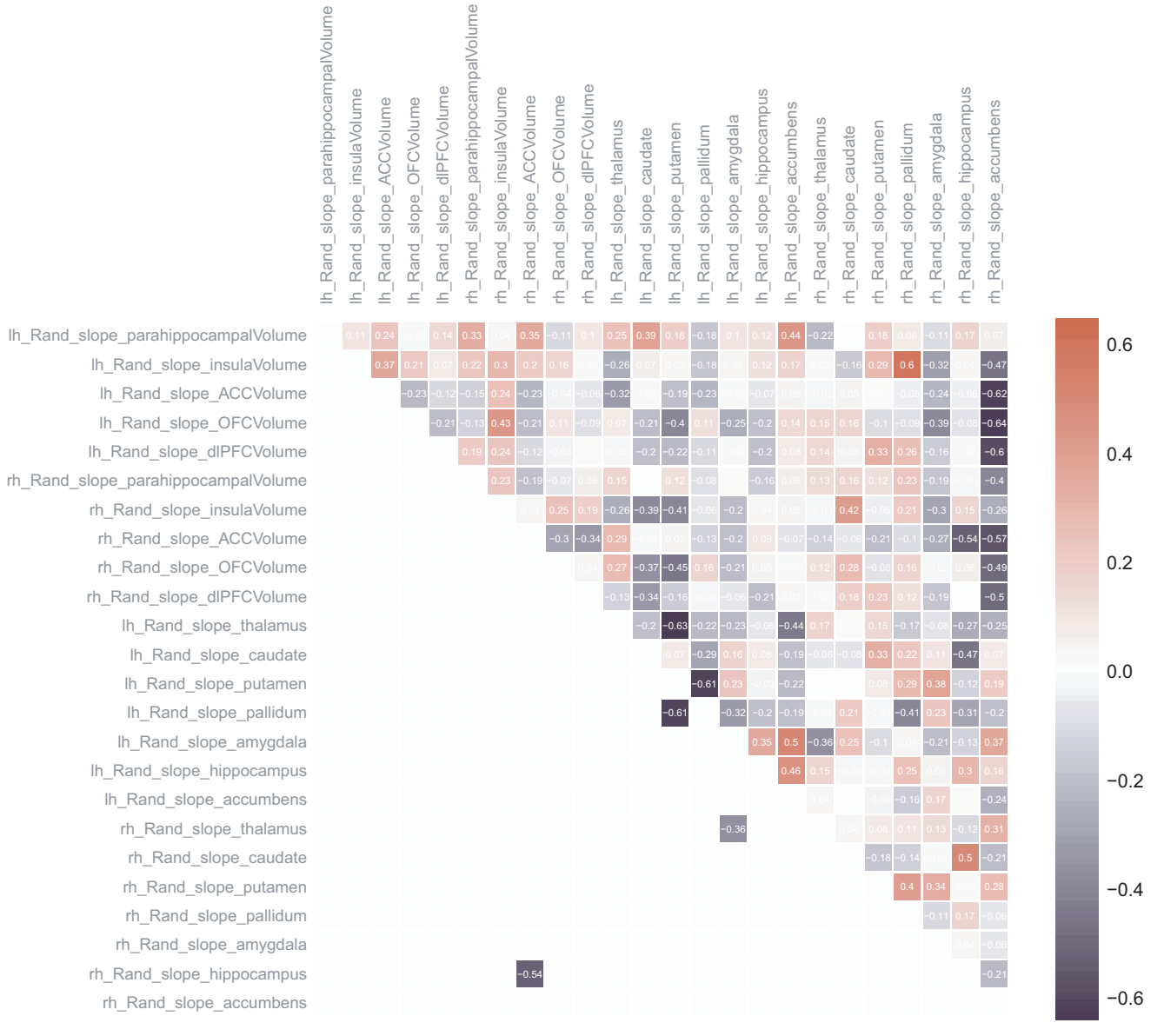

Figure 3 Difference matrix for rates of anatomical change (High parent-reported aggression group vs. low parent-reported aggression group). Significant differences are depicted in the lower half of the matrix

Smaller right hippocampal volume was associated with higher parent-reported aggression scores. Interestingly, follow-up analyses showed that this relation was driven by *change* in hippocampal volume regardless of initial volume of hippocampus at TP1; reinforcing the idea that longitudinal measures capture trajectories that cannot be observed using cross-sectional analyses. Stronger decline in hippocampal volume was related to increases in parent-reported aggression. Our findings demonstrated that hippocampal development and externalizing behavior coincide, yet we cannot infer the causal direction of this relation. Traditionally it is suggested that brain development shapes behavior, but it is likely that this shaping process goes both ways. Indeed, a recent study reported that externalizing behavior merely affects subcortical brain structure, and this relation was not found the other way around (Muetzel et al., 2017).

The hippocampus is part of the limbic system of the brain, which is generally involved in emotional processes. It has been suggested that the hippocampus plays an important role in regulating aggressive behavior. For example, regional stimulation of hippocampus can facilitate or inhibit aggression (Gregg & Siegel, 2001). Our finding that developmental changes in hippocampal volume were associated with developmental changes in externalizing behavior is also in line with findings of a previous longitudinal study with adolescents. Oostermeijer et al. (2016) showed that adolescents who displayed a desisting pathway of conduct problems showed aberrant development of hippocampal volume. Yet, it remains elusive whether our observed coinciding developmental pattern is related to deviant behavior. Our participants showed only mild problems of externalizing behavior, all within the healthy range of psychological functioning. Nevertheless, prior

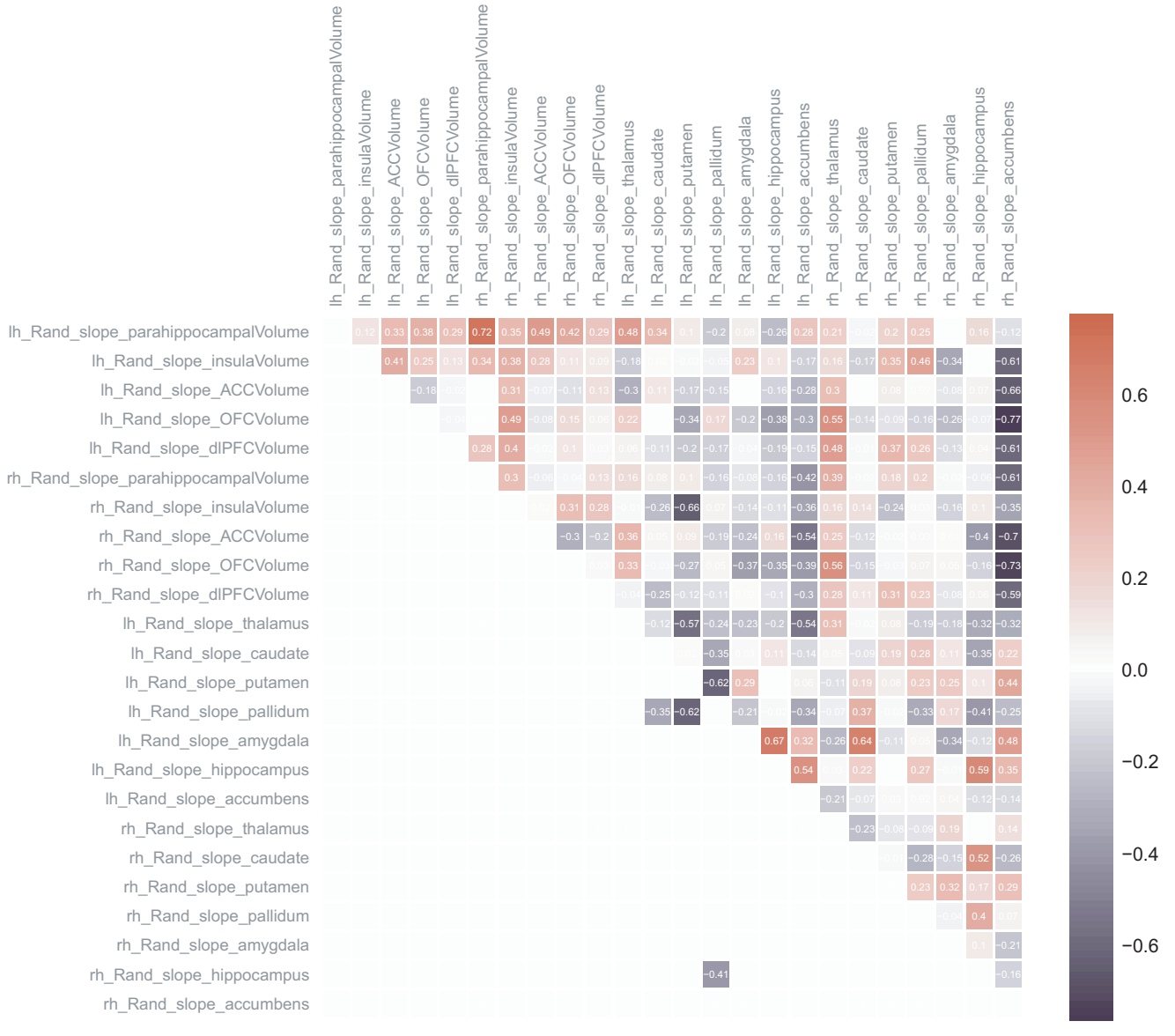

Figure 4 Difference matrix for rates of anatomical change (High parent-reported rule-breaking group vs. low parent-reported rule-breaking group). Significant differences are depicted in the lower half of the matrix

studies in clinical samples showed volumetric reductions of hippocampal volume in individuals with borderline personality disorder (Zetzsche et al., 2007) and conduct disorder (Huebner et al., 2008), which supports the idea that using a dimensional approach in a community sample may enhance our understanding of clinical externalizing problems.

It should be noted that hippocampal volume development was related to parent-reported aggression, but not to self-reported aggression. Parent-reported aggression and self-reported aggression correlated moderately in the current study indicating both substantial overlap as well as distinction between these two behavioral constructs.

In contrast to our expectation, we did not find relations between cortical thickness of dlPFC, OFC, and ACC and parent-reported nor self-reported aggressive behavior. Our results showed that parent-reported rule-breaking showed a negative relation with cortical thinning in right OFC and left dlPFC; although these results did not survive correction for multiple comparisons. Previous cross-sectional and longitudinal studies using both clinical and community samples emphasized the relation between cortical thickness of prefrontal regions and externalizing behavior (Ameis et al., 2014; Oostermeijer et al., 2016; Yang & Raine, 2009). Speculatively, differences in severities of externalizing behavior, age-range, and methodological differences (e.g., analytical approach of sMRI) may explain inconsistencies between studies.

Exploratory analyses on maturational coupling showed that adolescents with low levels of parent-reported aggressive behavior showed stronger synchronous development of right hippocampal volume and right ACC volume. This finding fits well with

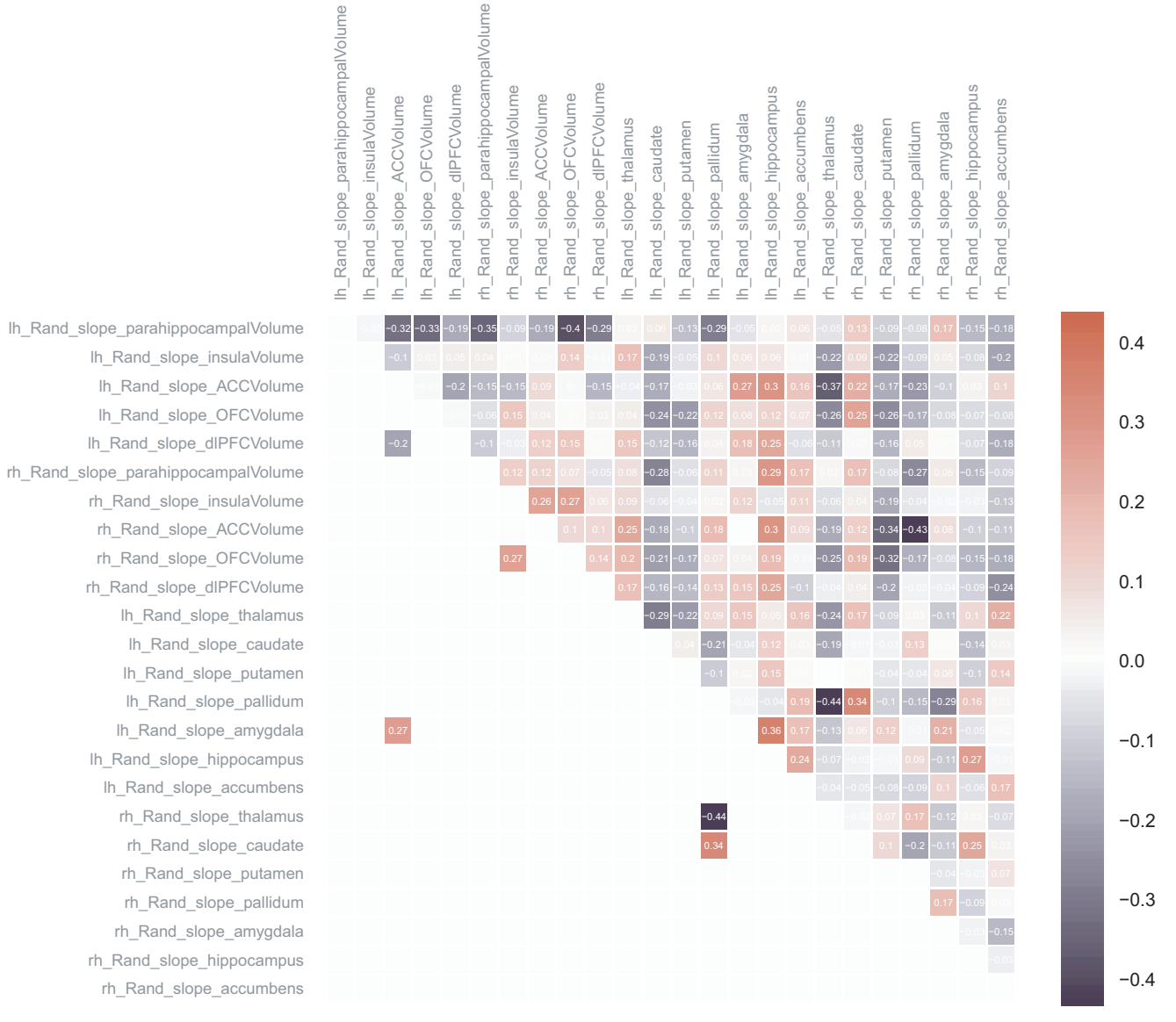

Figure 5 Difference matrix for rates of anatomical change (High self-reported aggression group vs low self-reported aggression group). Significant differences are depicted in the lower half of the matrix

prior longitudinal research that revealed similar outcomes for stronger amygdala-prefrontal cortex structural connectivity in relation to lower levels of psychopathology (Ameis et al., 2014; Vijayakumar et al., 2017). Given that previous research focused on specific ROIs, future research needs to examine whether externalizing behavior is related to maturational coupling within certain regions of the limbic system (e.g., amygdala and/or hippocampus) and prefrontal cortex, or whether a more general limbic system-prefrontal cortex network is involved.

Furthermore, we found that stronger maturational coupling was not merely related to lower levels of externalizing behavior. Adolescents with higher levels of parent-reported aggression and parent-reported rule-breaking showed stronger maturational coupling between the striatum and limbic system. Moreover, higher levels of self-reported aggression were related to stronger subcortical-subcortical coupling and cortical-subcortical coupling. Future research is warranted to replicate this pattern of mixed positive and negative associations between externalizing behavior and maturational coupling.

This study also had some limitations that should be addressed in future research. First, the sample is large in comparison to prior studies, but relatively small to test for age interactions. Second, the behavioral assessments included both the parent-report and self-report and were therefore multi-informant, but these informants did not report on exactly the same behavioral construct. In future studies, it will be important to better align measurements to have a general index of externalizing/aggressive behavior and to test whether results of different informants tap into different constructs and

subsequently distinct neural underpinnings. Third, we used a normative sample and none of the participants reported clinical levels of externalizing behavior. Future studies could benefit from examining the full range of externalizing behavior. Last, we only examined the relation between externalizing behavior and brain development without considering other factors that might contribute to this relationship. That is, during adolescence, substantial changes occur in several domains that might mediate this relationship, for example, social factors including not only school transitions and friendships, but also biological factors such as sex steroid hormones (Nguyen et al., 2016).

To conclude, this study revealed that aspects of externalizing behavior were associated with lower right hippocampal volume. Furthermore, we found that a stronger maturational network between ACC and limbic system was associated with low externalizing behavior, whereas stronger subcortical-subcortical maturational coupling was associated with relatively higher levels of externalizing behavior. Our findings highlight the need to investigate dynamic changes in brain structure and their relation to behavioral outcomes using within-person comparisons as well as examining developmental trajectories between regions. Unraveling the neural underpinnings of externalizing behavior across a continuum may provide important new insights about when normative development becomes deviant.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplementary methods.

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Key points

- Most evidence of structural brain abnormalities associated with externalizing behavior in adolescence is based on cross-sectional studies.
- Longitudinal designs are pivotal to understand how these brain abnormalities emerge.
- In the current study, we followed a community sample of participants aged 8–29 years (n = 271) over a period of 5 years (680 scans).
- We demonstrated that the developmental trajectory of hippocampal volume was negatively associated with the developmental trajectory of externalizing behavior.
- Externalizing behavior was linked to maturational coupling within cortico-subcortical regions.
- These findings add to our understanding of biological mechanisms associated with externalizing behavior and may provide theoretical implications to improve future prevention and intervention programs.

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